existence and strength of negative feedback mechanisms, set the threshold of AKT activation in a given setting. The cellular levels of FKBP51 appear to be another major factor in dictating this threshold. As for downstream signaling, is there a specific target of AKT that is particularly dependent on the elevated levels of AKT activity provided by increased S473 phosphorylation and that dictates the development of chemoresistance? Although there are many candidate pathways, previous studies on mouse tumor models suggest that mTOR complex 1 (mTORC1) activation can drive chemoresistance in response to increased AKT signaling (Wendel et al., 2004). Finally, in addition to the mechanistic questions above, it will be important to determine whether FKBP51 levels provide a clinical biomarker predicting whether a given tumor should be targeted with chemotherapeutics alone or in combination with emerging inhibitors of the PI3K-AKT pathway.

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SDH5 Mutations and Familial Paraganglioma: Somewhere Warburg is Smiling

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Paragangliomas have been linked to mutations affecting the succinate dehydrogenase complex. In a recent issue of *Science*, Rutter and coworkers showed that SDH5 is required for the flavination of SDHA, which is necessary for SDH assembly and function. Moreover, they detected SDH5 mutations in a large kindred with familial paraganglioma.

Otto Warburg observed decades ago that cancer cells display high rates of glycolysis, with the subsequent conversion of pyruvate to lactate, even when oxygen is available for the far more efficient production of ATP via the conversion of pyruvate to acetyl-CoA and subsequent oxidation via the Krebs cycle. How cancer cells establish this pattern of "aerobic glycolysis" is becoming clearer. For example, many oncogenic mutations activate mTOR, which in turn induces HIF1α. HIF1α transcriptionally activates many genes that promote glucose uptake and glycolysis. HIF1α also induces PDK1, which phosphorylates pyruvate dehydrogenase and thereby inhibits the entry of pyruvate into the Krebs cycle (Kroemer and Pouyssegur, 2008). Finally, HIF1α induces BNIP3, which promotes mitochondrial autophagy, and transcriptionally suppresses genes required for mitochondrial biosynthesis (Kroemer and Pouyssegur, 2008; Zhang et al., 2008). Another insight came with the recent discovery that cancer cells preferentially express the M2 isoform of pyruvate kinase, which is inhibited by the increased tyrosine kinase signaling typical of many cancer cells, leading to decreased oxidative phosphorylation and enhanced lactate production (Vander Heiden et al., 2009).

"Why," as opposed to "how," cancers resort to aerobic glycolysis is less clear, however. One possibility stems from the observation that unicellular organisms replicate their DNA and undergo cell division while engaged in reductive, rather than oxidative, metabolism, possibly to limit damage from endogenous reactive oxygen species (ROS) (Tu and McKnight, 2007). Perhaps aspects of this ancient coupling of metabolism to proliferation are still "hard-wired" in metazoans, in which case the shift to aerobic glycolysis might be more conducive for cell proliferation. It has also been proposed that glycolysis enhances the production of the building blocks necessary for anabolism (Kroemer and Pouyssegur, 2008; Vander Heiden et al., 2009). Nonetheless, Warburg's contention that altered metabolism caused cancer was gradually

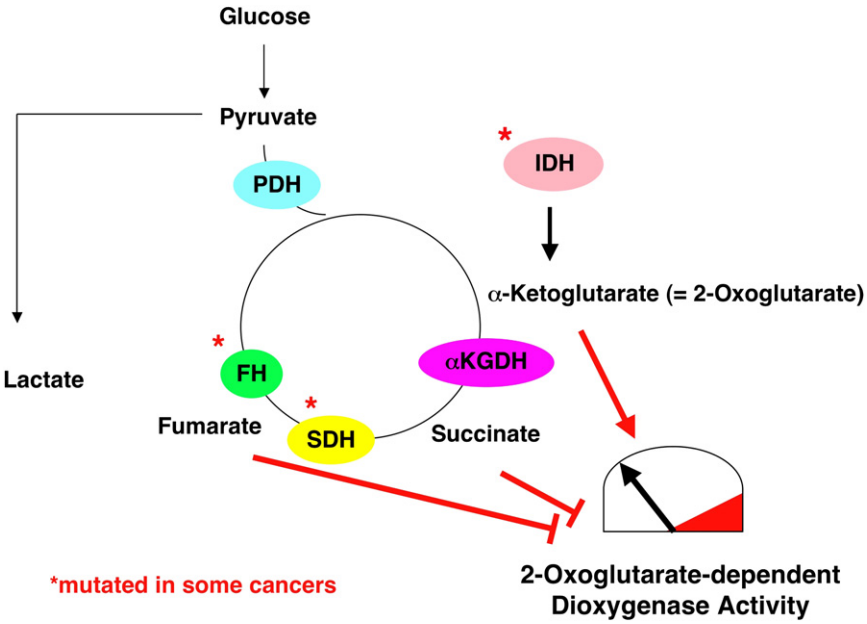

Figure 1. Potential Links Between Krebs Cycle and 2-Oxoglutarate-dependent Dioxygenase Activity

For simplicity, individual subunits of multimeric complexes are not shown. Increased activity (red triangle in meter) of certain 2-oxoglutarate-dependent dioxygenases, such as the proapoptotic prolyl hydroxylase PHD3 (EglN3), is envisioned to suppress tumor formation. Mutations affecting SDH or FH promote the accumulation of succinate and fumarate, respectively, which suppress the catalytic activity of 2-oxoglutarate-dependent dioxygenases.

supplanted by the idea that cancer is caused by mutations, some of which lead, as a consequence, to altered metabolism.

Interest in Warburg's observations has been rekindled, however, with the recent discovery that the Krebs cycle components succinate dehydrogenase (SDH) and fumarate hydratase (FH) are targets of germline mutations that cause hereditary paragangliomas (PGL) and papillary renal carcinomas, respectively (Vander Heiden et al., 2009). Moreover, somatic mutations affecting isocitrate dehydrogenase 1 and 2, which normally convert isocitrate to the Krebs cycle-intermediate α-ketoglutarate, have been described in some brain tumors (Vander Heiden et al., 2009). These genetic studies prove that metabolic deregulation can cause cancer.

SDH is a heteroligomer containing the subunits SDH A, B, C, and D and mutations of subunits B, C, and D have been linked to hereditary paragangliomas (PGL4, PGL3, and PGL1 syndromes, respectively). Rutter and coworkers, appreciating that many mitochondrial proteins are relatively uncharacterized, honed in on an evolutionarily conserved yeast mitochondrial protein, which they now call SDH5 (Hao et al., 2009). They found that SDH5 binds to SDHA (SDH1 in yeast) and, at least indirectly, promotes its flavination. Flavination of SDH1, for reasons that are not yet clear, is required for SDH complex assembly and function. Loss of SDH5 in yeast decreases the abundance of the other SDH components, probably caused by enhanced degradation as a result of altered SDH complex formation. SDH converts succinate to fumarate and also participates in the electron transport chain. Both of these activities are diminished in yeast lacking SDH5 and can be complemented with the human SDH5 ortholog (hSDH5). Some familial paraganglioma families (PGL2) display linkage to 11q13.1, which is the location for hSDH5. Rutter and coworkers identified a nonsynonomous hSDH5 variant in one such family and confirmed that it was defective with respect to SDH1 flavination and restoration of SDH activity when introduced into Δsdh5 yeast, implying that SDH5 mutations, like mutations affecting SDH subunits B, C, and, D, cause paraganglioma by abrogating SDH activity.

How might loss of SDH or FH cause cancer? Two nonmutually exclusive mechanisms have been put forth. Many 2-oxoglutarate-dependent enzymes have now been identified, including the PHD (also called EglN) prolyl hydroxylases that promote HIFα polyubiquitinylation and degradation and the FIH1 asparaginyl hydroxylase that inhibits HIFα transactivation function. The catalytic activity of these enzymes is coupled to the decarboxylation of 2-oxoglutarate (also called α-ketoglutarate) to succinate and is inhibited in the presence of excess succinate or the closely related molecule fumarate, such as occurs upon SDH and FH inactivation, respectively (Figure 1). Moreover, loss of SDH or FH activity has been reported to increase mitochondrial ROS production, which also inhibits dioxygenase function (Guzy et al., 2008; Sudarshan et al., 2009). A caveat, however, is that not all investigators have detected an increase in ROS production in SDH-defective mammalian cells (Cervera et al., 2008; Lee et al., 2005; Selak et al., 2006). Nonetheless, it is clear that SDH and FH mutations activate HIF, indicating that SDH and FH mutations compromise the function of the PHD dioxygenases, leading to a state of "pseudohypoxia" (Dahia et al., 2005; Isaacs et al., 2005). HIF activation, for the reasons stated above, would enhance glycolysis while potentially further decreasing flux through the Krebs cycle. Moreover, HIF can promote the transformation of certain cell types, as best demonstrated by the critical role of HIF2α in clear cell renal carcinomas linked to loss of the von Hippel-Lindau protein. It is intriguing that FH mutations cause kidney cancer (albeit with papillary rather than clear cell histology) and that SDH mutations have also been detected in kidney cancer, suggesting that renal epithelial cells might be particularly susceptible to HIF-induced transformation.

Many other 2-oxoglutarate-dependent dioxygenases are also involved in cancer-relevant processes such as extracellular matrix formation (for example, the collagen prolyl and lysyl hydroxylases), RNA splicing (Jmjd6), and chromatin structure (for example, the JmjC-containing histone demethylases). Such proteins might also couple Krebs cycle metabolism to transformation. Complicating matters further, many of these proteins are encoded by HIF-responsive genes, presumably to compensate for diminished availability of

their required oxygen donor under hypoxic conditions. Thus, these enzymes form an oxygen and metabolism-responsive network.

Why are SDH mutations linked to a small subset of tumors (primarily paragangliomas) rather than a wide variety of tumors? One hypothesis relates to the embryological origins of paragangliomas, which are tumors of the sympathetic nervous system. During embryological development, an excess number of neuroblasts with the potential to become sympathetic neurons are generated. These cells then compete with one another for growth factors such as NGF, with the losers undergoing apoptosis. PHD3 (EglN3) appears to be both necessary and sufficient for apoptosis in this setting, which appears to be largely HIF independent (Lee et al., 2005). Loss of SDH activity, for reasons outlined above, blunts PHD3-induced apoptosis. Likewise, the other genes linked to familial paraganglioma (including NF1, c-Ret, and VHL) ultimately impact upon this pathway, suggesting that paragangliomas arise because certain neuronal precursors elude development culling (Lee et al., 2005). This model would explain why somatic SDH mutations are relatively rare in sporadic paragangliomas unless accompanied by a previously unsuspected, germline, SDH mutation (similar rules apply to NF1, c-Ret, and VHL in this setting).

The discovery of SDH, FH, and IDH mutations has renewed hope that cancer cell metabolism can be exploited therapeutically. Some progress has been made toward identifying targets that are particularly important for the survival of highly glycolytic tumor cells. In addition, 2-oxoglutarate-dependent dioxygenases can be reactivated with drug-like molecules (Kroemer and Pouyssegur, 2008). The development of a successful cancer therapeutic along these lines would be further testimony to the vision of Otto Warburg.

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